



## Anti-TNF-induced autoimmune hepatitis

To the Editor:

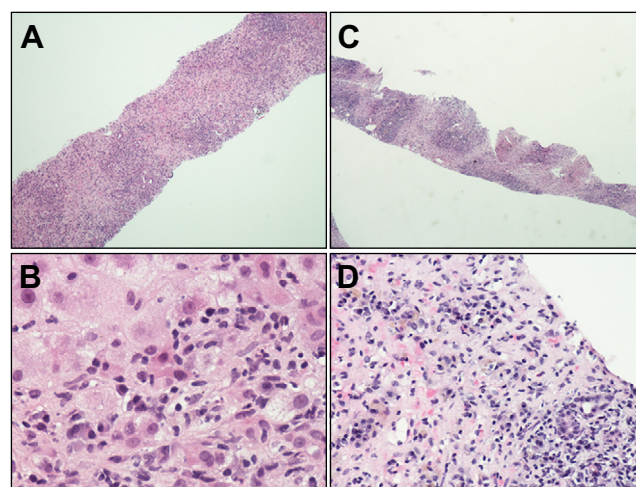
We read with interest the report by Weiler-Normann *et al.* [1] evaluating the safety and efficacy of infliximab as a rescue therapy in difficult-to-treat autoimmune hepatitis (AIH). TNF-targeted therapies are widely used for treating a rapidly growing number of autoimmune diseases. However despite their effectiveness in many of these diseases, there have been increasing reports of autoimmune processes developing *de novo* after their use, including AIH. This is highlighted by our experience with two cases of severe anti-TNF therapy-induced AIH.

The first patient, a 60-year-old woman with a 20-year history of rheumatoid arthritis, treated with prednisone 5 mg/day, with remote exposure to methotrexate (MTX). She presented with elevated liver enzymes four months after treatment with adalimumab, which had been normal prior to anti-TNF therapy. Her liver enzymes were grossly abnormal with ALT 923 IU/L (normal <40 IU/L), AST 1146 IU/L (normal <32 IU/L), bilirubin 76  $\mu$ mol/L (normal <20  $\mu$ mol/L), INR 1.1 (normal 0.9–1.1), and albumin 36 g/L (normal 33–48 g/L). Anti-nuclear antibody (ANA) was positive, documented prior to initiation of anti-TNF therapy, anti-smooth muscle antibody (ASMA) negative, and IgG level normal at 15.52 g/L (normal 6.80–18.00 g/L). ds-DNA antibodies were highly positive. Despite discontinuing adalimumab, over the following month she developed features of progressive liver failure with INR 1.8, albumin 16 g/L, bilirubin 271  $\mu$ mol/L, pruritis, and progressive lower extremity edema. There was no hepatic encephalopathy. Fibroscan® showed a liver stiffness of 33.3 kPa (IQR 4.8 kPa; 100% success). Liver biopsy showed features consistent with AIH, including expansion of portal areas with dense plasma cell infiltrates, prominent interface activity, and bridging necrosis (Fig. 1A and B). Prednisone 40 mg/day was started in combination with azathioprine 50 mg/day. Liver enzymes completely normalized within 8 weeks of treatment. Serial fibroscans showed a striking improvement in liver stiffness, with her most recent liver stiffness measure of 5.4 kPa (IQR 0.9 kPa; 77% success). She remains in biochemical remission and is currently being reconsidered for alternative anti-TNF therapy for management of her rheumatoid arthritis.

The second patient is a 48-year-old woman with an 18 year history of rheumatoid arthritis. She was treated with MTX and naproxen, both of which were discontinued in November 2010 due to elevated ALT (158 IU/L). Liver enzymes completely normalized following drug withdrawal (ALT 19 IU/L; June 2011). In July 2011 she was started on infliximab (IFX) 5 mg/kg and after 12 months of therapy she was admitted to hospital with hepatic failure with INR 1.6, albumin 22 g/L, bilirubin 408  $\mu$ mol/L, ALT 505 IU/L, AST 1614 IU/L, and moderate ascites. She had no hepatic encephalopathy. ANA was positive (negative prior to treatment with IFX), ASMA negative, and IgG level elevated at 27.8 g/L. Liver biopsy showed features consistent with severe AIH including submassive hepatic necrosis with plasma cell rich inflammation and significant fibrosis (Fig. 1C and D). Fibroscan® revealed a liver stiffness of 24.6 kPa (IQR 14.4; 63% success). IFX was

discontinued and prednisone started at 50 mg/day in combination with azathioprine 50 mg/day. Biochemical remission occurred after 8 weeks of treatment. Repeat Fibroscan® after 14 months of treatment showed a marked improvement in liver stiffness (6.2 kPa; IQR 1.4; 100% success). She was recently started on tocilizumab (IL-6 receptor antagonist) with close monitoring of liver enzymes.

Biological agents are increasingly used in the treatment of autoimmune diseases, however a growing number of reports have outlined the paradoxical induction of autoimmune processes. To date there have been roughly 20 cases of drug-induced autoimmune liver injury reported with anti-TNF therapy [2], with the majority of cases occurring between one month to one year after initiation of anti-TNF therapy [3]. Anti-TNF-induced AIH has occurred most commonly with IFX and much less commonly with adalimumab or etanercept [4]. Most patients respond completely to anti-TNF withdrawal and treatment with corticosteroids, with a few cases of spontaneous recovery with drug withdrawal alone [4]. Overall prognosis is favorable, and normalization of liver enzymes generally rapid. There is however a single report of a patient requiring liver transplantation after developing severe cholestatic hepatitis related to IFX [5]. Treatment with an alternative TNF antagonist after resolution of the liver injury appears to be generally well tolerated, without recur-



**Fig. 1. Liver biopsies demonstrating typical features of AIH.** Liver biopsy from the first patient, after four months treatment with adalimumab, shows expansion of portal areas due to predominant plasma cell infiltrate with prominent interface inflammatory activity and bridging necrosis (A and B). Liver biopsy from the second patient, after twelve months treatment with infliximab, shows massive hepatic necrosis with almost complete destruction of hepatocytes within the sampled tissue, portal triad expansion with connective tissue, bile duct proliferation and predominant lymphoplasmacytic cell infiltrate (C and D). (This figure appears in colour on the web.)

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## Letters to the Editor

rence [4,6–8]. Whether anti-TNF-induced liver damage reflects drug-induced immune-mediated liver injury, or induction of *de novo* autoimmune hepatitis remains controversial [9]. Typically, liver biopsies from these patients exhibit many of the classical features of AIH, and immunosuppressive therapy is typically required for resolution of liver inflammation [4–8]. However, the lack of chronicity or disease relapse on withdrawal of immunosuppression favors drug-induced immune-mediated liver injury.

Although anti-TNF-induced AIH is uncommon, it is being increasingly described. We report two cases of severe AIH associated with anti-TNF therapy. In both cases, the patients responded to withdrawal of anti-TNF therapy and immunosuppressive treatment. Our cases and other reports of anti-TNF-induced AIH, coupled with the recent report by Weiler-Normann *et al.* [1], highlight important paradoxical clinical effects of anti-TNF therapy; having the capacity to both ameliorate and induce AIH. A number of studies have defined both pro-inflammatory and anti-inflammatory effects of TNF, mainly through the differential activation of the two TNF receptors (TNFR1 and TNFR2) expressed on T cells [10]. Specifically, TNF can activate effector T cell function, mainly through TNFR1, which drives inflammatory responses [10,11]. In contrast, TNF stimulation of TNFR2 expressed on regulatory T cells expands the highly suppressive pool of these cells, which in turn prevents autoimmunity and attenuates inflammation [11]. Therefore, anti-TNF therapy may either induce or suppress autoimmune inflammatory responses by altering the balance between effector and regulatory T cell activation [11]. In addition, differential hepatic immune responses to anti-TNF therapy may also be influenced by host genetics and the hepatic microenvironment (e.g., cytokine milieu, TNFR expression profile, cellular sources of TNF). These potential explanations for the opposing effects of anti-TNF therapy in liver autoimmunity should be examined in future studies in this field.

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## Reply to: “Anti-TNF-induced autoimmune hepatitis”

To the Editor:

We would like to thank Dr. Borman [1] and colleagues for their case presentations illustrating the potentially harmful impact of anti-TNF-agents on the liver: In this case in their ability to induce autoimmune hepatitis (AIH). We have previously shown that infliximab, one of the anti-TNF-drugs, may successfully treat AIH in selected difficult-to-treat cases [2].

It is well known, that autoimmune features may occur during treatment with anti-TNF-agents, especially the emergence of anti-dsDNA-antibodies has been described in up to 30% of the patients [3]. Yet, not all patients who develop autoantibodies will also develop clinical symptoms or disease. Further on, most patients at risk are likely to have a strong genetic back-

### Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Meredith A. Borman  
Stefan Urbanski  
Mark G. Swain\*

Faculty of Medicine, Division of Gastroenterology and Hepatology,  
University of Calgary, Calgary, Alberta, Canada

\*Corresponding author.

E-mail address: [swain@ucalgary.ca](mailto:swain@ucalgary.ca)

ground for the development of autoimmune diseases as anti-TNF-agents are primarily used to treat autoimmune diseases. Therefore, it seems necessary to discriminate between *de novo* autoimmune diseases in genetically prone patients and paradoxical inflammation that may also develop as a consequence of use of these agents. Especially for infliximab, the oldest among the recombinant antibodies (and unlike etanercept as a soluble receptor also binding to cell-bound TNF), a wide number of immunological side effects have been described [4], among others psoriasis-like lesions, lupus like syndrome, systemic lupus erythematoses, (paradoxical) joint inflammation, (*de-novo*) inflammatory bowel disease, uveitis as well as different forms of vasculitis [5].